REMARKS

In the application, Claims 1- 31 are pending. The Examiner has withdrawn Claims 25-27 from consideration, indicating that they are subject to a restriction requirement, and rejected Claims 1-24 and 28-31. In view of the Examiner's comments, the claims have been amended as set forth above. Applicants now request reconsideration of the application as amended.

Improper Request for Continued Examination

It has been noted that the prior office action was mistakenly designated as final by the Examiner. Applicants are contacting Kendall Jones as the Examiner has suggested.

Election/Restrictions

The Examiner has indicated that new claims 25-27 are directed to an invention that is independent or distinct from the invention originally claimed, and he has withdrawn these claims from consideration in this application.

Applicant respectfully traverses the restriction and withdrawal of the claim on the grounds that claims 25 - 27 are directed to same invention as that claimed in claims 1-24 and 28-32. In each case (claims 1-24, 28-32, and claims 25-27), the claimed method is one for combinatorially (i.e., artificially) controlling gene expression by controlling DNA binding affinity and DNA binding site by varying the composition of one or more cis-regulatory regions (or sequences). As described in the specification at page 15, lines 11-22, "Altogether, there are six "programmable" degrees of freedom: the binding thresholds [etc.]. . . By making different selections for these six variables, a number of gene regulatory logics can be implemented." (Emph. added.) This passage describes how the composition is varied, as illustrated by the equations at the end of the same paragraph and the following sections, which describe how each logic function is implemented. For example, Equation 9 describes the conditions (total statistical weight of all states) under which expression is ON or OFF for calculating the probability of promoter occupation (see Equation 3) when using a logical OR function. These conditions are determined by the variables binding thresholds n_A, n_B, the Boltzmann weight for promoter occupancy, q_0, and the mutual cooperativity factors ω_{AB}. Because the logic functions are implemented by selection of the variables that are described as the programmable degrees of freedom, it is respectfully submitted that the method claims in claims 25-

27 are not directed to a distinct invention but to the same invention as claimed in claims 1-24 and 28-32. To emphasize the clear relation between the claims, claim 25 has been amended to include that the specified conditions *correspond to inputs into one or more logic functions, wherein the one or more logic functions are selected according to a relationship between the two or more transcription factors and a disease or condition.* It is also brought to the Examiner's attention that claim 26 lists that same logic functions that are specified in the other claim sets and, therefore, clearly involves implementation of logic functions.

In view of the foregoing, the Examiner is requested to remove the restriction and to consider claims 25-27 along with the other pending claims.

Withdrawn Objections/Rejections

The Examiner has withdrawn his rejection under §103(a) of claims 1, 3, 5, 7-8, 11, 13, 15 and 17-18 as being unpatentable over Bujard et al. in view of Wasiewicz et al., in further view of Kirch et al. in view of Orkin.

The Examiner has also withdrawn his rejection under §103(a) of claims 2 and 12 as being unpatentable over Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin, and further in view of Kirchhamer et al.

The Examiner has also withdrawn his rejection under §103(a) of claims 4, 6, 14 and 16 as being unpatentable over Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin, and further in view of Renkawitz.

The Examiner has also withdrawn his rejection under §103(a) of claims 9 and 19 as being unpatentable over Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin, and further in view of Ogawa.

35 U.S.C. § 101

The Examiner has rejected Claims 1-24 and 28-31 under 35 U.S.C. § 101 as being directed to non-statutory subject matter. In particular, the Examiner is of the opinion that no physical transformation occurs, and that the steps are performed in a computer.

Applicants respectfully submit that the invention is not directed to an *in silico* transformation or to any operation performed by a computer.

In support of his rejection, the Examiner refers to page 27, lines 6-14 of the specification which states in its entirety as follows:

> The transcription apparatus appears to be a natural computing machine. The machine is effectively a general-purpose computer with a function that can be "programmed" at will through choices and placements of the protein-binding DNA sequences in the regulatory region. This can be contrasted with the alternative strategy of transcription control based on dedicated, complex (e.g., allosteric) molecular interactions. In the latter scheme, complexity of the system is derived from the complexity of proteins, while in the former, complexity is derived combinatorially from the composition of the regulatory sequences (the "software"), without the need for manipulating the proteins (the "hardware").

This language says that the method of the invention produces control of genetic functions that causes it to act something like a computer, i.e., it "*appears* to be a natural computing machine" -- it is not an actual computer. This paragraph provides only an analogy to illustrate how the inventive method makes it possible to control or program genetic responses in cells by exercising transcription control.

In fact, the claims *do* provide a practical application -- that of providing a way to produce a desired gene expression in response to the presence of regulatory proteins (transcription factors) that are indicative of a disease or a condition. The desired gene expression is not one that would occur in nature -- it is engineered to have a practical application that either generates an indication of the presence of the disease or condition based on the presence of the transcription factors or triggers expression of a genetic treatment, either in the form of activating a "killer gene" or activating a drug receptor for targeted administration of a drug. These are real and useful functions, not abstract calculations that can be implemented *in silico*. To clarify the intended result of the claimed method, each of the independent claims has been amended to include the following limitation: "wherein the desired genetic response in the cell comprises reporting or treatment of the disease or condition in which the two or more transcription factors (regulatory proteins) are expressed."

It is respectfully submitted that the claims as amended are directed to statutory subject matter. The Examiner is requested to withdraw the rejection under §101.

35 U.S.C. §112

The Examiner has rejected claims 1-20 and 28-31 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner identifies the language at lines 9-13 of claim 1 as being indefinite and states that it is unclear how, in the case of a singular logic function, there is implementation of both sets of interactions. As pointed out above in Applicant's comments about the restriction requirement, the logic functions are implemented by selection of various combinations of values of the degrees of freedom: DNA binding thresholds for each transcription factor $\tilde{n}$, Boltzmann weight for promoter occupancy q_0, and mutual cooperativity factors ω between the transcription factors and RNA polymerase. Implementation of even the most simple OR function is not merely a matter of detecting the presence of either A or B. The resulting expression level for an OR function is determined by the probability of promoter occupancy (see Equation (3), page 12), which is determined by the statistical weight of all states in which the promoter is occupied (Z_{ON}) or unoccupied (Z_{OFF}):

$$Z_{OFF} = 1 + q_A + q_B + q_A q_B$$

$$Z_{ON} = q_0(1 + \omega q_A + \omega q_B + 2\,\omega q_A\, q_B),$$

where q_A and q_B are the ratios of the transcription factor concentrations n to the binding thresholds $\tilde{n}$ for each of transcription factor (inputs) A and B. (See page 15, lines 11-22). To clarify, the independent claims have been amended to specify that the variables are selected "to control the probability of promoter occupancy". The probability of promoter occupancy is what determines regulated recruitment. As described in the specification at page 26, 2nd paragraph, regulated recruitment is achieved using continuously tunable protein-DNA binding strengths and glue-like contact interaction between proteins.

The Examiner also finds lines 15-18 of claim 1 and lines 13-16 of claim 11 to be unclear. Each claim has been amended to clarify that the relationship second form of control is cooperative or competitive binding *between* the TFs and the polymerase. Whether the binding is cooperative or competitive will depend on the nature of the logic function and the desired result. For example, if the desire is to prevent gene expression when two TFs are present above a specified threshold, there will be competitive binding with the polymerase.

The Examiner finds the phrase in claim 11, "unique gene expression that does not normally occur under the conditions corresponding to the two or more inputs", to be indefinite. In response, the language has been amended to specify that the result is a "unique and artificial genetic response", meaning that the genetic response would not occur but for the artificial manipulation of the degrees of freedom that control the probability of promoter occupancy.

The examiner rejects claim 11 due to lack of antecedent basis for the limitation "the conditions". The amendment discussed in the paragraph above addresses this issue.

35 U.S.C. §103

Rejection #1

The Examiner has reiterated his rejection of Claim 21 under 35 U.S.C. §103 as being unpatentable over Bujard et al. (U.S. Patent 5,814,618) in view of Wasiewicz et al. (*Cybernetics and Systems: An International Journal*, volume 31, 2000, pages 283-315).

Applicants respectfully submit that Bujard et al. describe regulation of gene expression that involves only a single chimeric protein that mixes different interaction domains together with the DNA binding domain of a specific regulator (TetR). In other words, Bujard, et al. teach only a single regulator. For purposes of illustration, call this regulator "A". In logic, (A AND A) will always be A; (A OR A) will always be A. Bujard et al. cannot possibly suggest a logic function that requires two or more inputs, each of which is a *different regulatory protein*. In Bujard et al., there is no requirement that two different conditions be present in a certain combination in order to produce a conditional result that is different for each logic function. Accordingly, Bujard et al. does not teach or suggest a logic function that operates on two or more different regulatory proteins to produce an output that is a unique gene expression as claimed.

Claim 21 has been amended to specify that (i) the selected relative binding strength and relative binding position "control the probability of promoter occupancy"; and (ii) that the "programmed gene expression in the cell comprises reporting or treatment of a disease or condition in which the two or more different regulatory proteins are expressed". Further, the gene expression resulting from each logic function is specified as different. Neither of these limitations is taught or suggested by Bujard et al.

The Examiner relies on Wasiewicz et al. for their teaching of a molecular computer and asserts that it would be obvious to modify the teachings of Bujard et al. with that of Wasiewicz et al. to arrive at the claimed gene computing method. Applicants respectfully disagree.

First, Bujard et al. does not teach or suggest a logic function. Using a specific combination of two polypeptides to form a single functional protein is addition, not a logical AND operation. The absence of the teaching of a logical operation by Bujard et al. would result in there being no basis for making a mental connection to the molecular computing taught by Wasiewicz et al.

Second, Bujard et al. describe modification of gene expression in a cell, i.e., *in vivo*. Wasiewicz et al. describe the use of different DNA sequences *in vitro* to *symbolize* rules in a knowledge tree. Nothing in Wasiewicz et al. suggests regulation of gene expression in a cell, or any possible *in vivo* application; DNA is merely a symbol -- a string of letters, that can be used to represent different rules depending on the sequence of those letters. Any arbitrary string of letters or symbols will suffice for this purpose; Wasciewicz et al. are simply taking advantage if the fact that symbols have already been assigned to each base and that bases can be organized as needed to create the desired combination. Computation using the molecular computer of Wasiewicz et al. requires laboratory processing to synthesize the DNA sequences, including annealing, ligation, and electrophoresis. There is no suggestion that these DNA sequences (inference paths) can be used as anything but unique strings of symbols that correspond to rules and are capable of replicating. There is no suggestion of regulation of gene expression in a cell by the DNA sequences used in this molecular computer, and the only mention of an *in vivo* operation is the potential use of bacteria to multiply the inference paths. Wasiewicz et al suggest no biological purpose for their computer such as reporting or treatment of a disease or condition. The only common ground between Bujard et al. and Wasiewicz is that DNA is somehow manipulated in both, but for entirely different reasons. In fact, these two references are so unrelated that there could be no reasonable connection made by one of skill in the art that would lead them to combine the references to render obvious Applicants' invention related to a method for producing programmed gene expression in a cell for reporting or treatment by implementing different logic functions on different inputs, each of which are regulatory proteins.

An important object of the present invention is to produce engineered promoters in cells by combining multiple different "cues" to induce a desired genetic response by regulated recruitment.

For example, one can program the regulatory sequences to turn on a reporter gene only if the pattern of regulatory protein activities (from two or more regulatory proteins) in a cell matches one of those unique to tumor cells. The reporter gene can then serve as the indicator of tumor cells and guide external treatment such as radiation or surgery.

The key to the invention is that the regulatory proteins are used combinatorially -- a combination of conditions must occur, i.e., regulators must be present under specified conditions to control the probability of promoter occupancy in order to obtain the desired gene expression, i.e., regulated recruitment. For example, by inserting a designed regulatory region controlling a reporter gene (e.g., the green fluorescent protein or GFP) into a population of bacteria equipped with a number of special chemical detectors, one can program these bacteria to look for and report unique patterns of detected traits that correspond to specific chemical pollutants or biological warfare agents in the environment. Alternatively, the reporter gene may be replaced by a therapeutic gene to target the conditions under which the regulatory proteins were produced, e.g., detection of proteins from tumor cells would trigger expression of genes to induce apoptosis. The use of multiple cues (different inputs) as opposed to a single cue, as taught by Bujard et al., makes discrimination possible, an essential component for successful gene therapy. The inventive method does much more that just increase the level of an otherwise expected expression as taught by Bujard et al.; it promotes "designer gene expression" that would not occur under normal conditions but for the programming that is done by way of adjustments to the cis-regulatory region by selecting values for the programmable degrees of freedom that determine the probability of promoter occupancy, as claimed.

Accordingly, it is respectfully submitted that the combination of Bujard et al. with Wasiewicz et al. fails to teach or suggest Applicants' invention as now claimed. The Examiner is requested to withdraw the §103 rejection of claim 21 over the cited combination.

Rejection #2

The Examiner has rejected Claims 1, 3-8, and 13-18 under 35 U.S.C. §103 as being unpatentable over Bujard et al. in view of Wasiewicz et al. as applied to Claim 21 above, in further view of Kirch et al. (*Oncogene*, 1999, volume 18, pages 2728-2738) in view of Orkin (*Cell*, volume

63, 1990, pages 665-672) in view of Renkawitz [*Trends in Genetics*, 1990, volume 6, pages 192-197] in view of Cho et al. [*Genes & Development*, 1998, volume 12, pages 2483-2487].

Kirch et al. is cited for its disclosure of synergistic activation of transcription and selective mutation of the sequence to reduce or eliminate transcription. Orkin is cited for its discussion of transcription at locus controlled regions that result in long distance interactions.

As discussed above, the combination of Bujard et al. with Wasiewicz et al. fails to teach or suggest a method for controlling gene expression by taking two or more different inputs, where each input comprises a regulatory protein, and performing a logic operation on the inputs to control the probability of promoter occupancy that will produce an output that is a desired gene expression in a cell, and where the logic operation is achieved by adjusting DNA binding strength and locating to select the types of interactions between the regulatory proteins and the interactive binding at the binding sites.

While Kirch et al. may teach an AND-like function as a result of the use of a combination of different motifs, it provides nothing to suggest that the same regulators can be combined by a different designer promoter, created by varying binding strengths and locations in cis-regulatory regions, to implement other logic functions, such as OR, NAND, or XOR, to drive a different gene expression in the same cell. Accordingly, Kirch et al. does not bring to a combination with Bujard et al. and Wasiewicz et al. what is missing from that combination. As such, the combination of the three references does not teach or suggest Applicants' invention as now claimed.

While Orkin may teach protein-protein interactions in regulating transcription control, it does not teach or suggest a plurality of different logic functions that can be implemented by various combinations of the two or more different regulatory proteins and adjustment of binding strengths and locations in cis-regulatory regions as claimed in the amended claims to produce a different genetic response in the cell. Because both Kirch et al. and Orkin fail to teach or suggest what is missing from the combination of Bujard et al. and Wasiewicz et al., the combination of the four references would not render Applicants' invention obvious to one of skill in the art. Accordingly, the combination of Bujard et al., Wasiewicz et al., Kirch et al. and Orkin fails to teach or suggest a method of combinatorially controlling transcription by implementing one of a plurality of different logic functions to produce different gene expression results in a cell as claimed.

The examiner relies on the article of Renkawitz for its discussion of transcriptional repression in eukaryotes and different types of cooperativity and competition. Specifically, the Examiner asserts that Figures 1 through 4 of Renkawitz demonstrate a subset of the multitude of different types of logic functions representing cooperative and competitive interactions in biomolecules.

Applicants acknowledge that Renkawitz illustrates different possible interactions between transcription factors and that Renkawitz describes basic responses that can occur when trans-activating factor are present. However, Renkawitz teaches little beyond what is already known or obvious from the previously cited references – that activation or blocking (repression) can occur under certain conditions. Nothing in Renkawitz teaches how artificial gene expression for reporting or treatment of certain conditions can be induced by programming the probability of promoter occupancy through the selection of relative binding strength and relative binding position, each of which is going to be different (different values and different combinations) for each of the one or more logic functions. It is respectfully submitted that the Examiner is interpreting the logic function to be a mere combination of binary values based on the inputs, each of which is either ON or OFF, present or absent. However, the fact that the probability of promoter occupancy is what is being controlled is clearly more than a simple matter of a combination of inputs being one or zero.

Cho et al. are relied on for their discussion of allosteric interactions between capping enzyme subunits and polymerase. Cho et al. teach complex molecular interactions which are derived from the complexity of proteins themselves, not from the combination of the regulatory sequences that can be manipulated by controlling the degrees of freedom that determine relative binding position and relative binding strength. As explained in the specification at page 27, 2nd paragraph, the present invention "can be contrasted with the alternative strategy of transcription control based on dedicated, complex (e.g., allosteric) molecular interactions. In the latter scheme, complexity of the system is derived from the complexity of proteins, while in the former, complexity is derived combinatorially from the composition of the regulatory sequences (the "software"), without the need for manipulating the proteins (the "hardware"). Accordingly, Cho et al. does not teach combinatorial control of transcription by controlling a probability of promoter occupancy to produce the desired response of reporting or treatment of a disease or condition in which the regulatory proteins are expressed.

Rejection #3

The Examiner has rejected Claims 2 and 12 under 35 U.S.C. §103 as being unpatentable over Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin in view of Rankawitz in view of Cho et al. as applied to Claims 1, 3-8, 11, 13-18 and 21 above, and further in view of Kirchhamer et al. (*PNAS*, volume 93, 1996, pages 9322-9328).

Kirchhamer et al. are cited for their disclosure of modular cis-regulatory organization, however, Kirchhamer et al. do not teach or suggest a method of combinatorially controlling transcription by implementing one of a plurality of different logic functions on two or more different inputs, each comprising a regulatory protein, to control a probability of promoter occupancy to produce a genetic response of reporting or treating a disease or condition in which the regulatory proteins (transcription factors) are expressed. As a result, combination of the teachings of Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz and Cho et al. does not render the claimed method obvious.

Rejection #4

The Examiner has rejected Claims 9 and 19 under 35 U.S.C. §103 as being unpatentable over Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin in view of Renkawitz in view of Cho et al. as applied to claims 1, 3-8, 11, 13-18 and 21 above, and further in view of Ogawa (U.S. Patent 5,535,382 issued July 9, 1996).

Ogawa is cited for its disclosure of the use of logic functions in minimal conjunctive normal form for ranking the results of a document retrieval system. It is respectfully submitted that Ogawa does not teach or suggest a method of combinatorially controlling transcription by implementing one of a plurality of different logic functions on two or more different inputs, each comprising a regulatory protein, control a probability of promoter occupancy to produce a genetic response of reporting or treating a disease or condition in which the regulatory proteins are expressed as claimed.. Furthermore, as there is nothing in either Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz, or Cho et al. alone, or any combination thereof, that provides any suggestion of attempting to implement a plurality of different logic functions acting on different inputs that are regulatory proteins for controlling the probability of promoter occupancy to produce a genetic

response of reporting or treating a disease or condition in which the regulatory proteins are expressed, there would have been no motivation to combine the teachings of Ogawa relative to a document retrieval system with any of Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz, and Cho et al. Accordingly, the stated combination would not render the invention as claimed in claims 9 and 19 obvious.

Rejection #5

The Examiner has rejected claims 10 and 20 under 35 U.S.C. §103 as being unpatentable over Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin in view of Renkawitz in view of Cho et al. in view of Ogawa as applied to claims 1, 3-9, 11, 13-18 and 21 above, and further in view of Gardner et al. (*Nature*, 2000, volume 403, pages 339-343).

For the reasons set forth in the preceding discussion, the combination of Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz, and Cho et al. with Ogawa does not render the claimed invention obvious, and, therefore the subject matter of claims 1, 3-9, 11, and 13-18 are patentable over the prior art. The combination of the seven listed references with Gardner et al., which teaches a genetic switch, still fails to teach or suggest the implementation of a plurality of different logic functions acting on different inputs that are regulatory proteins for controlling the probability of promoter occupancy to produce a genetic response of reporting or treating a disease or condition in which the regulatory proteins are expressed.

A switch is either "on" or "off"; it does not perform logic functions, nor does it teach how to control transcription by combining two or more regulatory proteins with a cis-regulatory region that has adjustable binding strengths and sites to selectively control the probability of promoter occupancy to induce different genetic responses in a cell. While it may ultimately be possible to implement combinatorial control of gene expression by creating a genetic circuit from a series of genetic switches, such an approach would require many operations with intermediate regulators before achieving the ultimate desired genetic response. This is distinguishable from the present invention, which designs cis-regulatory control so that the final gene expression output is derived from one step of the levels of the input regulators without the need for intermediate regulators and gene expression. Accordingly, the teachings of Gardner, et al. would not render Applicants'

invention obvious when combined with the teachings of Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz, Cho et al. and Ogawa .

Rejection #6

The Examiner has reiterated his rejection of claim 22 under 35 U.S.C. §103 as being unpatentable over Bujard et al. in view of Wasiewicz et al., as applied to claim 21 above, and further in view of Kirchhamer et al.

For the reasons previously stated, the combination of Bujard et al. in view of Wasiewicz et al. fails to teach or suggest Applicants' invention as claimed in claim 21 as amended.

Kirchhamer et al. are cited for their disclosure of modular cis-regulatory organization, however, Kirchhamer et al. do not teach or suggest a method of combinatorially controlling transcription by implementing one of a plurality of different logic functions acting on different inputs that are regulatory proteins for controlling the probability of promoter occupancy to produce a genetic response of reporting or treating a disease or condition in which the regulatory proteins are expressed. As a result, combination of the teachings of Kirchhamer et al. with that of Bujard et al. in view of Wasiewicz et al. does not render the method of claim 21 obvious and therefore cannot render the subject matter of dependent claim 22 obvious.

Rejection #7

The Examiner has reiterated his rejection of claims 23-24 under 35 U.S.C. §103 as being unpatentable over Bujard et al. in view of Wasiewicz et al., as applied to claim 21 above, and further in view of Orkin.

The Examiner relies on Orkin for its disclosure of protein-protein interactions in regulating transcription control. However, Orkin does not teach or suggest a plurality of different logic functions acting on different inputs that are regulatory proteins for controlling transcription to produce a different genetic response for each logic function as claimed in claim 21.

For the reasons previously stated, the combination of Bujard et al. in view of Wasiewicz et al. fails to teach or suggest Applicants' invention as claimed in amended claim 21. Because Bujard et al. and Wasiewicz et al. do not disclose a method for combinatorial control of transcription by implementing one of a plurality of different logic functions acting on different inputs that are

regulatory proteins for controlling the probability of promoter occupancy to produce a genetic response of reporting or treating a disease or condition in which the regulatory proteins are expressed, it is respectfully submitted that the claimed invention would not be obvious to one of skill in the art because Orkin does not disclose what is missing from Bujard et al. in view of Wasiewicz et al.. Since claims 23 and 24 depend from claim 21, they are similarly non-obvious.

Rejection #8

The Examiner has rejected Claims 28-29 under 35 U.S.C. §103 as being unpatentable over Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin in view of Renkawitz in view of Cho et al. as applied to Claims 1, 3-9, 11, 13-18 and 21 above, and further in view of Matthews et al. (U.S. Patent 5,717,058).

The Examiner relies on Matthews et al. for their teaching of transcriptional methods for cancer and activation of reporter genes and killer genes.

While it is acknowledged that the object of Matthews et al.'s method and that of the present invention is generally the same, i.e., the treatment of disease through transcription control, Matthews et al. direct their work toward identification of specific peptides that can be introduced to inhibit Tax-mediated transcription by disrupting protein-protein interactions . Matthews et al. do not teach or suggest a method of *combinatorially* controlling transcription by implementing one of a plurality of different logic functions acting on different inputs that are regulatory proteins for controlling the probability of promoter occupancy by varying the composition of the binding site. Since the claimed method is missing from the teachings of Matthews et al., Matthews et al. cannot contribute to the combined teachings of Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz and Cho what that combination lacks in order to render Applicants' invention obvious as claimed in claim 1. Accordingly, claims 28 and 29, which depend from claim 1 are not obvious.

Rejection #9

The Examiner has rejected Claims 30-31 under 35 U.S.C. §103 as being unpatentable over Bujard et al. in view of Wasiewicz et al. in view of Kirch et al. in view of Orkin in view of Renkawitz in view of Cho et al. as applied to Claims 1, 3-9, 11, 13-18 and 21 above, and further in view of Ross et al. (*Journal of Bacteriology*, 1989).

The Ross et al. article is relied on for its discussion of introduction of an external material (mercury) and the resultant increase in expression of a mercury resistance gene to assist in treatment of mercury poisoning.

Ross et al. teach that mutations of the regulatory protein bind at different locations and, thus, produce different transcriptional activation functions. There is nothing to suggest variation of the binding strengths and binding locations in the cis-regulatory regions to modify their composition to produce different interactions between two or more regulatory proteins and between the two or more regulatory proteins and polymerase. Since the claimed method is missing from the teachings of Ross et al., it is not possible for Ross et al. to contribute to the teachings of the combination of Bujard et al., Wasiewicz et al., Kirch et al., Orkin, Renkawitz and Cho what that combination lacks in order to render Applicants' invention as claimed in claim 1 obvious. Accordingly, claims 30 and 31, which depend from claim 1 are not obvious.

It is respectfully submitted that the claims as amended above distinguish the invention from the cited prior art and that the invention patentably distinct. The Examiner is respectfully requested to withdraw all rejections under §103 and allow all claims as now presented.

New Claims

New claims 32 - 44 are added in the amended claim set. Claims 32 - 39 add claims corresponding to previously submitted claims 28-31 that depend from independent claims 11 and 21, respectively.

Support for new claims 40 - 44 can be found in the specification as follows (with reference to the application as published):

Claim	Support (US 2006/0051838 A1)
40	[0038], Equation 3; [0045]
41	[0050], Equation 10; [0045]
42	[0047], Equation 9; [0045]
43	[0057], Equation 12; [0045]
44	[0053], Equation 11; [0045]

Amendment to the Title

The title has been amended to better reflect the subject matter as claimed.

Conclusion

It is believed that all grounds for rejection have been addressed and overcome. The Examiner is respectfully requested to reconsider the claims as amended, withdraw the objections and rejections, and issue a notice of allowance of all claims now pending in the application.

Should the Examiner believe that prosecution of this application might be expedited by further discussion of the issues, he is requested to telephone the undersigned attorney for Applicants at the telephone number indicated below.

Respectfully submitted,

Dated: January 6, 2009

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